Amendment to the Specification

1. Please enter the enclosed Sequence Listing at the end of the specification.

2. Please replace the following numbered paragraphs of the specification.

[17] Fig. 1. Synthetic compounds and mechanistic schemes. a, Designed protein kinase bisubstrate analog inhibitors. Compound 1 was synthesized and studied by Gibson and colleagues[8] as a potential PKA inhibitor. Compound 2 was designed based on a dissociative transition state for phosphoryl transfer. Distance between the anilino nitrogen and the gamma- phosphorus was calculated using Chem3D assuming an extended conformation of the acetyl linker. The peptide sequence is derived from IRS72727. Compound 3 was prepared to evaluate the relative contribution of the peptide residues toward inhibition. b, Scheme illustrating associative vs dissociative transition states for phosphoryl transfer. ROH is the nucleophile (tyrosine phenol in this work) attacking the g-phosphoryl group of ATP, and ADP is the leaving group. Associative transition state (path A) in this work is defined as more than 50% bond formation between the nucleophilic oxygen and the phosphorus, which occurs with at least 50% leaving group residual bond formation present. Dissociative transition state (path B) in this work is defined as less than 50% bond formation between the nucleophile and the phosphorus, which occurs before the leaving group-phosphorus bond is at least 50% broken. c, Synthetic scheme toward the preparation of bisubstrate analog 2. R1 = AcNH-Lys-Lys-Lys-Leu-Pro-Ala-Thr-Gly-Asp- (SEQ ID NO: 3); R2 = -Met-Asn-Met-Ser-Pro-Val-Gly-Asp-CO2H (SEQ ID NO: 4); R3 = R1 with side chain protected residues; R4 = R2 with side chain protected residues and Asp linked to Wang resin.

[22] Fig. 4 shows the synthesis and structure of the kemptide-ATP(S conjugate as an inhibitor of protein kinase A. R_1=AcNH-Leu-Arg-Arg-Ala- (SEQ ID NO: 6), R_2=-Leu-Gly-COOH, R_3=R_1 with Arg protecting groups; R_4=R_2 with Gly linked to Wang resin.

[28] Bisubstrate inhibitors typically contain a second moiety which is a peptide having residues similar to that of the natural protein substrates of the particular protein kinase. Such peptides can be determined for each additional protein kinase by methods known in the art, including but not limited to library-based techniques[22, 23]. One peptide useful for the insulin receptor kinase is known in the art and called irktide (Lys, Lys, Lys, Leu, Pro, Ala, Thr, Gly, Asp, Tyr, Met, Asn, Met, Ser, Pro, Val, Gly, Asp (SEQ ID NO:1)). A peptide useful for protein kinase A is known in the art and called kemptide (Leu, Arg, Arg, Ala, Ser, Leu, Gly (SEQ ID NO:2)). Peptides can be modified as described in more detail below. The peptide moieties of the bisubstrate inhibitors need not contain all of the amino acid residues identified above. Fewer may be required than the total. Thus as few as 4, 5, 6, or 7 of the amino acid residues may be sufficient to provide the requisite specificity. In addition, the residues may be modified to improve their access to cells. For example, membrane translocating sequences are known in the art and can be appended to the peptides of the bisubstrate inhibitors. One such sequence is AAVALLPAVLLALLAP (SEQ ID NO:~~3~~ 5) See *J. Bio. Chem. 270:* 14255, 1995 and *Nature Biotech. 16:* 370, 1998. Such sequences can be advantageously placed at the N-terminal or C-terminal. A Human Immunodeficiency Virus TAT sequence can also be used to improve access to cells by the bisubstrate inhibitors. See Schwarze *et al.*, *Science 285:*1569, 1999. One means of stabilizing the peptide sequence is to substitute carbon-carbon bonds in place of amide bonds. Other suitable replacements include that of NH with O (depsipeptide), use of urethane moieties to replace one or more amino acid residues, and the use of peptoids to replace amino acid residues. See *J. Med. Chem. 37:*2678 (1994) and *Angewandte Chemie Int'l Ed. 34:*907 (1995). Such peptides, peptoids, peptidomimetics are within the contemplation of the invention and are referred to herein as peptide moieties.

Respectfully submitted,

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